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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/758,303	01/14/2004	Yi-You Huang	DF-03500	5393

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EXAMINER	
YANG, NELSON C	

ART UNIT	PAPER NUMBER
1641	

DATE MAILED: 05/04/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/758,303	HUANG ET AL.	
	Examiner	Art Unit	
	Nelson Yang	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 March 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10 and 12-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-10, 12-14 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 November 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 1/14/04
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

1. Applicant's amendment of claims 1, 10, 13 is acknowledged and has been entered.

2. Applicant's cancellation of claims 11, 15-22 is acknowledged and has been entered.

3. Claims 1-10 and 12-14 are currently pending.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claim 1 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claim recites detecting said amplified signal via a nanogold probe and a quantum dot. However, support for this limitation could not be found in the disclosure, which only provides support for detecting said amplified signal via a nanogold probe **or** a quantum dot. Currently, it is believed that the limitation was intended to be interpreted as detecting said amplified signal via a nanogold probe or a quantum dot. However, if applicant actually did intend for the claim to be interpreted as detecting said amplified signal via a nanogold probe and a quantum dot, it would be appreciated if applicant could point out the support for this limitation in the specification.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

7. Claims 1-3, 5, 7, 10 are rejected under 35 U.S.C. 102(e) as being anticipated by Labaer et al [US 6,800,453].

With respect to claim 1, Labaer et al teach a method in which an antibody can be covalently bound to a derivatized substrate, e.g., using a crosslinker, e.g., N-hydroxy-siccinimidyl ester. The test polypeptides with epitopes such as Flag, HA, or myc are then bound to antibody-coated plates (column 57, lines 55-66). Nucleic acids disposed on the array can be amplified directly on the array by using primers (column 72, lines 48-65) and using rolling circle amplification (RCA) (column 18, lines 46-57). Labaer et al further teach that the nucleic acid tags can be coupled to insoluble substrates such as nanoparticles (column 59, lines 22-41) and comprise materials such as gold (column 54, lines 30-31).

8. With respect to claims 2-3, Labaer et al teach specific classes of binding pairs such as peptide epitopes and monoclonal antibodies, where one member of the binding pair is attached to the substrate (column 57, lines 43-56).

9. With respect to claim 5, Labaer et al teach a nucleic acid that includes a test amino acid sequence and an affinity tag to which a binding agent recognizes (column 2, lines 11-20), where the affinity tag can be a free cysteine (column 58, lines 45-50).

10. With respect to claim 7, each address of the plurality is provided with a nucleic acid, e.g., by pipetting, spotting, printing (e.g., with pins), piezoelectric delivery, or, e.g., other means of mechanical delivery. In a preferred embodiment, the provided nucleic acid is a template nucleic acid, and the method further includes amplifying the template, such as by rolling circle amplification (column 18, lines 46-57).

11. With respect to claims 10, Labaer et al further teach that the nucleic acid tags can be coupled to insoluble substrates such as nanoparticles (column 59, lines 22-41) and comprise materials such as gold (column 54, lines 30-31).

Claim Rejections - 35 USC § 103

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. Claims 1-4, 6-10, 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lizardi et al [US 6,143,495] in view of Strathmann [US 6,480,791].

With respect to claim 1, Lizardi et al teach a method for amplifying nucleic acid sequences based on the presence of a specific target sequence or analyte with high specificity and sensitivity (column 2, lines 64-67). By coupling a nucleic acid tag such as open circle probes

(OCP) to a specific binding molecule, such as an antibody, rolling circle amplification of the nucleic acid tag can be used to detect analytes in a sample (column 3, lines 17-26). Rolling circle amplification is accomplished by a rolling circle replication primer that is complementary to the primer complement portion of the OCP (column 13, lines 23-30). To aid in detection and quantitation of nucleic acids amplified using RCA and RCT, detection labels can be directly incorporated into amplified nucleic acids or can be coupled to detection molecules (column 13, lines 57-61). Detection labels include radioactive isotopes, fluorescent molecules, phosphorescent molecules, enzymes, antibodies, and ligands (column 14, lines 1-5), all which could be considered to be nanoparticles. Lizardi fails to teach the use of a quantum dot, using a fluorescence label rather than a quantum dot (column 14, lines 1-5).

Strathmann, however, does teach the use of quantum dots for labeling and further discloses that reaction products may be amplified (col. 31, lines 55-65) and that polynucleotides may be visualized in several different ways including use of fluorescent and quantum dot labels (col. 35, lines 3-13).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the fluorescent labels in the Lizardi et al. invention with quantum dots because Strathmann teaches that fluorescent labels and quantum dots are functional equivalents as nucleic acid labels.

14. With respect to claims 2-3, Lizardi et al teach specific binding molecules such as an antibody (column 3, lines 17-26), which would bind to antigens.

15. With respect to claim 4, the rolling circle replication primer contains a complementary portion between 10 to 35 nucleotides long and can also contain a non-complementary portion that is 1-100 nucleotides long (column 13, lines 30-55).

16. With respect to claim 6, Lizardi et al teach open circle probes comprising target probe portions, primer complement complement portions, spacer region, detection tag portions secondary target sequence portions, address tag portions, and promotion portions (column 8, lines 38-50), as well as amplification target circles containing between 40 to 1000 nucleotides comprising primer complement portions, detection tag portions, secondary target sequence portions, address tag portions, and promoter portions (column 12, lines 45-55). Lizardi et al also teach the use of DNA polymerase (column 21, lines 8-11), nucleotides (column 222, lines 10-40), and buffers (column 60, lines 20-30).

17. With respect to claims 7, 9, Lizardi et al teach open circle probes comprising primer complement complement portions (column 8, lines 38-50), as well as amplification target circles containing between 40 to 1000 nucleotides comprising primer complement portions (column 12, lines 45-55).

18. With respect to claim 8, Lizardi et al teach that in RCA, a rolling circle replication primer hybridizes to circular OCP or ATC molecules followed by rolling circle replication of the OCP or ATC molecules using a strand-displacing DNA polymerase, wherein rolling circle replication results in large DNA molecules containing tandem repeats of the OCP or ATC sequence (column 30, lines 25-51).

19. With respect to claim 10, Lizardi et al teach that to aid in detection and quantitation of nucleic acids amplified using RCA and RCT, detection labels can be directly incorporated into

amplified nucleic acids or can be coupled to detection molecules (column 13, lines 57-61). Detection labels include radioactive isotopes, fluorescent molecules, phosphorescent molecules, enzymes, antibodies, and ligands (column 14, lines 1-5), all which could be considered to be nanoparticles.

20. With respect to claim 12, Lizardi et al teach that the length of the oligonucleotides in the detection probes can be 10 to 35 nucleotides long (column 15, lines 12-30).

21. Claims 1-4, 6-10, 12, 13, 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lizardi et al [US 6,143,495] in view of Mirkin et al [US 6,361,944], and further in view of Natan et al, [6,579,726].

With respect to claims 1, 13, 14, Lizardi et al teach a method for amplifying nucleic acid sequences based on the presence of a specific target sequence or analyte with high specificity and sensitivity (column 2, lines 64-67). By coupling a nucleic acid tag such as open circle probes (OCP) to a specific binding molecule, such as an antibody, rolling circle amplification of the nucleic acid tag can be used to detect analytes in a sample (column 3, lines 17-26). Rolling circle amplification is accomplished by a rolling circle replication primer that is complementary to the primer complement portion of the OCP (column 13, lines 23-30). To aid in detection and quantitation of nucleic acids amplified using RCA and RCT, detection labels can be directly incorporated into amplified nucleic acids or can be coupled to detection molecules (column 13, lines 57-61). Detection labels include radioactive isotopes, fluorescent molecules, phosphorescent molecules, enzymes, antibodies, and ligands (column 14, lines 1-5), all which could be considered to be nanoparticles. Lizardi fails to teach the use of a quantum dot, using a

fluorescence label rather than a quantum dot (column 14, lines 1-5). Lizardi et al fail to teach the use of spherical nanogold particles.

Mirkin et al however teach that oligonucleotides functionalized with alkanethiols at their 5'-termini readily attach to gold nanoparticles (column 17, lines 15-20) and is well characterized (column 17, lines 8-14). Natan et al further teach that DNA can be detected utilizing metal nanoparticles that are preferably spherical (column 13, lines 31-43) and further teaches that the use of such nanoparticles leads to an 100,000 fold increase in sensitivity using detection means such as SPR (column 3, lines 40-45).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the 5' end of the oligonucleotides with an –SH group as taught by Mirkin et al in the invention of Lizardi et al, as Mirkin et al. teach that such a modification provides the advantage of strongly attaching the oligonucleotides to the gold nanoparticles. It would also have been obvious to one of ordinary skill in the art at the time the invention was made to utilize spherical gold nanoparticles, as taught by Natan et al, in the method of Lizardi et al in order to achieve a 100,000 fold increase in sensitivity using detection means such as SPR.

22. With respect to claims 2-3, Lizardi et al teach specific binding molecules such as an antibody (column 3, lines 17-26), which would bind to antigens.

23. With respect to claim 4, the rolling circle replication primer contains a complementary portion between 10 to 35 nucleotides long and can also contain a non-complementary portion that is 1-100 nucleotides long (column 13, lines 30-55).

24. With respect to claim 6, Lizardi et al teach open circle probes comprising target probe portions, primer complement complement portions, spacer region, detection tag portions

secondary target sequence portions, address tag portions, and promotion portions (column 8, lines 38-50), as well as amplification target circles containing between 40 to 1000 nucleotides comprising primer complement portions, detection tag portions, secondary target sequence portions, address tag portions, and promoter portions (column 12, lines 45-55). Lizardi et al also teach the use of DNA polymerase (column 21, lines 8-11), nucleotides (column 222, lines 10-40), and buffers (column 60, lines 20-30).

25. With respect to claims 7, 9, Lizardi et al teach open circle probes comprising primer complement complement portions (column 8, lines 38-50), as well as amplification target circles containing between 40 to 1000 nucleotides comprising primer complement portions (column 12, lines 45-55).

26. With respect to claim 8, Lizardi et al teach that in RCA, a rolling circle replication primer hybridizes to circular OCP or ATC molecules followed by rolling circle replication of the OCP or ATC molecules using a strand-displacing DNA polymerase, wherein rolling circle replication results in large DNA molecules containing tandem repeats of the OCP or ATC sequence (column 30, lines 25-51).

27. With respect to claim 10, Lizardi et al teach that to aid in detection and quantitation of nucleic acids amplified using RCA and RCT, detection labels can be directly incorporated into amplified nucleic acids or can be coupled to detection molecules (column 13, lines 57-61). Detection labels include radioactive isotopes, fluorescent molecules, phosphorescent molecules, enzymes, antibodies, and ligands (column 14, lines 1-5), all which could be considered to be nanoparticles.

28. With respect to claim 12, Lizardi et al teach that the length of the oligonucleotides in the detection probes can be 10 to 35 nucleotides long (column 15, lines 12-30).

29. Claims 13, 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Labaer et al [US 6,800,453], in view of Mirkin et al [US 6,361,944] and further in view of Natan et al, [6,579,726].

Labaer et al. disclose the invention substantially as claimed, as discussed above. Labaer et al fail to teach the use of spherical nanogold particles.

Mirkin et al however teach that oligonucleotides functionalized with alkanethiols at their 5'-termini readily attach to gold nanoparticles (column 17, lines 15-20) and is well characterized (column 17, lines 8-14). Natan et al further teach that DNA can be detected utilizing metal nanoparticles that are preferably spherical (column 13, lines 31-43) and further teaches that the use of such nanoparticles leads to an 100,000 fold increase in sensitivity using detection means such as SPR (column 3, lines 40-45).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the 5' end of the oligonucleotides with an –SH group as taught by Mirkin et al in the invention of Labaer et al because Mirkin et al teach that such a modification provides the advantage of strongly attaching the oligonucleotides to the gold nanoparticles. It would also have been obvious to one of ordinary skill in the art at the time the invention was made to utilize spherical gold nanoparticles, as taught by Natan et al, in the method of Lizardi et al in order to achieve a 100,000 fold increase in sensitivity using detection means such as SPR.

Response to Arguments

30. Applicant's arguments filed March 1, 2006 have been fully considered but they are not persuasive.

31. Applicant's arguments on p.4 that the presently claimed invention and the teachings of Labaer et al are completely different methods for detecting peptides array are not found persuasive. It should be noted that the limitations cited by applicant in the arguments, specifically "a capture molecule coupled to a specific nucleic acid sequence", such that "when recognizing the target, using the rolling circle amplificatioin amplifies the specific nucleic acid sequence, and using the nanogold coupling to a complementary nucleic acid sequence binds to the amplified nucleic acid sequence, and then observes the result" have not been recited by applicant in the claims. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., using the nanogold coupling to a complementary acid sequence binds to the amplified nucleic acid sequence) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Since Labaer et al do teach all the claims currently recited in the claims, the claims currently read upon the prior art.

32. In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the

applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). Strathmann shows that quantum dots and fluorescent labels are equivalent structures known in the art for labeling nucleic acids for amplification processes, as discussed above. Therefore, because these two labels were art-recognized equivalents at the time the invention was made, one of ordinary skill in the art would have found it obvious to substitute quantum dots for fluorescent labels.

33. Applicant also argues that Mirkin et al do not teach modifying the 5' end of oligonucleotides with an –SH group. As discussed above, Mirkin et al do teach oligonucleotides functionalized with alkanethiols at their 5'-termini readily attach to gold nanoparticles (column 17, lines 15-20) and is well characterized (column 17, lines 8-14). In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

34. In response to applicant's argument that one of the benefits of the present invention is that the experimental result could be observed by the naked eyes, the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985).

Conclusion

35. No claims are allowed.

36. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

37. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nelson Yang whose telephone number is (571) 272-0826. The examiner can normally be reached on 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long V. Le can be reached on (571)272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

38. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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9/28/06